PREDICTION OF QUALITY ATTRIBUTES OF CONTINUOUSLY PRODUCED GRANULES USING COMPLEMENTARY PAT TOOLS

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ABSTRACT

Manufacturers of pharmaceutical solid dosage forms aim for a reduced production time and a shorter 'time-to-market'. Therefore continuous manufacturing gains increasing interest in the pharmaceutical industry. For continuous manufacturing, the quality of produced pharmaceuticals should be assessed in real-time (in-line, on-line and at-line) and not via the traditional off-line, often destructive and time-consuming analysis methods which supply the desired information only hours after sampling. This research paper evaluates three Process Analytical Technology (PAT) tools for the real-time at-line analysis of granules, which were produced using a continuous wet twin-screw granulator being part of a from powder-to-tablet production line (ConsiGma™-25). A Raman and NIR spectrometer were used together with a photometric imaging technique in order to acquire solid state information and granule size data. These multivariate data were then used to predict the granules' moisture content, tapped and bulk density and flowability. The three PAT tools provided complementary information for predicting these quality attributes of the continuously produced

granules. The residual moisture content was mostly correlated with the spectroscopic data, whereas the imaging-data had the highest predictive capability for the flowability of the granules.

KEYWORDS: Continuous wet granulation – granule quality attributes prediction – Raman spectroscopy – NIR spectroscopy – Photometric imaging

INTRODUCTION

Nowadays, the pharmaceutical industry aims at shifting its manufacturing of solid dosage forms from batch production towards continuous production. The ideal continuous process should be capable of producing both small amounts of product (e.g. lab scale or clinical scale) as well as full production scale [1]. Hence, the time-consuming, labor-intensive and expensive scaling-up studies can be avoided. Consequently, the production time of solid dosage forms will shorten and the time-to-market will decrease significantly. Whereas for batch production the actual processing time is only two days, the total elapsed time can take up to 60 days [2]. The protracting delays in between the different processing steps of a batch process are eliminated using a continuous production line. Furthermore, continuous manufacturing lines are designed to be fully automated, so the lines can produce 24 hours a day in a “lights-out” manner. Other important advantages are that continuous pharmaceutical manufacturing equipment requires less floor space and less energy.

Granulation is often used in the pharmaceutical industry as an intermediate step prior to tabletting to improve the processability of the starting powder materials. Compared to powders, granules flow better, produce less dust, have a higher density and segregate less [3]. A number of quality attributes can therefore be defined for granules such as flow properties, mechanical durability, porosity, particle size and residual moisture content.

With regard to flow properties several off-line tests for the determination of the flowability of granules exist. For example, the dry funnel method measures the time a weighted amount of

powder/granules needs to fall through a funnel. Another example is the ring-shear tester, which has a specially designed large shear cell for granules, and the working principles have been described in literature [4]. Tapped and bulk density measurements allow to calculate the Hausner ratio (HR) of the inspected powder or granules (HR = tapped density/bulk density). According to the classification, a Hausner ratio higher than 1.25 indicates that powders or granules are flowing poorly. The residual moisture content of granules is mostly determined via Karl Fischer titration or loss on drying measurements.

The currently applied conventional quality control systems are often based on sampling and time-consuming off-line analyses in analytical laboratories, and they annul the advantages of continuous processing. Continuous manufacturing requires continuous evaluation of the critical process and formulation quality attributes *during* processing. Therefore this study aims to rapidly assess granule size, roughness and solid-state information using at-line photometric imaging and Raman and NIR spectroscopy during continuous granulation. These data are then used to calculate and predict the critical granule attributes namely flowability and residual moisture content.

Several non-destructive measurement techniques have been recently developed for the (in-process) determination of granule size distributions. Spatial Filtering Velocimetry (SFV) measures simultaneously particle size and velocity of flowing material as it passes through a laser beam, causing shadows onto a linear array of optical fibers. This technique was already applied in both twin-screw [5] and fluid bed granulation [6]. Another technique using a laser beam on moving particles is Focused Beam Reflectance Measurement (FBRM). Here, a moving particle will cause backscattering of the laser light back into the probe and hence the chord length of the particle can be calculated. An FBRM probe, equipped with a mechanical scraper to avoid fouling, was used for the monitoring of a high shear wet granulation process [7]. Liew et al. [8] captured the particle movement in a fluid bed coater by means of a high-speed video camera. Dynamic digital image processing (Camsizer, Retsch Technology) was used by Patchigolla and Wilkinson [9] for the size and

shape monitoring during glutamate-crystallization. Naervanen et al. [10] reconstructed three-dimensional topographic images by means of red, green and blue led light illumination. These topographic data were then used to calculate the size of separate granules. They managed to monitor trends of the median granule size during fluid bed granulation processing. Yu and Hancock [11] evaluated the ability of a dynamic imaging analysis (DIA) technique (QicPic, Sympatec) for adequate particle size and particle shape determination. They evaluated both spherical and rod-shaped samples with the DIA and compared them with laser diffraction and scanning electron microscopy respectively. This DIA apparatus has been used to determine the particle size and particle shape of both powders [12] and granules [13] in order to predict the flowability of the investigated particles.

In this study, photometric stereo imaging (FlashSizer FS3D) [14] was used for the evaluation of the granule size distribution, the roughness and the shape of continuously produced wet granules. The technique is based on the illumination of the sample with two different white-light sources which are placed in an angle of 180° in a horizontal plane. These two images are then combined in order to obtain a 3D surface image of the measured sample. The surface images are not only used to determine the particle size distribution and the particle shape, but the digital images give information about the surface roughness as well. Therefore the image is seen as a combination of pixels, every pixel being a spatial coordinate with a certain light intensity. The grey level of this brightness of the pixel is then characterized with a value, going from 0 to 255, 0 being totally black and 255 fully white. The surface roughness calculation is based on differences in the grey scale values. Soppela et al. [15] evaluated the ability of photometric stereo imaging (FlashSizer 3D) for particle size and flowability measurements of granules. Furthermore, the particle size determination was compared with SFV (Parsum®) and conventional sieving.

NIR spectroscopy has been extensively studied for moisture analysis of granules. For instance, Hartung et al. [16] used NIR spectroscopy for the in-line moisture monitoring during a spray drying

and tabletting process of enalapril maleate. The in-line moisture measurements were then used to evaluate the influence of moisture on the final tablet hardness. To study the end-point of a fluid-bed drying cycle, a PLS-model was developed in order to predict the moisture content by means of in-line NIR-spectra, with loss on drying as reference method [17]. Nieuwmeyer et al. [18] did similar work, using Karl Fischer as a reference method. Furthermore, based on the same NIR-spectra a PLS-model was built in order to predict the median granule size. In-line NIR-measurements for residual moisture prediction have already been performed on the ConsiGma™-system [19]. Only a limited amount of tests was performed, which was covering a small range of residual moisture content (0.43-1.06 % w/w). NIR spectroscopy in combination with multivariate data analysis has also been investigated in order to predict the flowability of both powders [20] and granules [21].

Multiple papers report on the usefulness of Raman spectroscopy in detecting changes in the API and excipient solid-state properties during pharmaceutical granulation processes. The API, theophylline, used in this present study has been thoroughly investigated during pharmaceutical processing. Theophylline can occur in several solid state forms during wet granulation and drying [22]. Anhydrous theophylline was mixed in the dry premix, and as expected, this was converted to theophylline monohydrate during wet granulation [5]. Drying induces the conversion from the hydrated form of theophylline to either anhydrous theophylline or a metastable form of theophylline, depending on the applied temperature and drying technique [23].

In the advent of increasing interest in continuous granulation in pharmaceutical manufacturing it is evident that studies are needed to assess the quality of the intermediate and final products. The present study aims to combine solid-state, moisture, granule size and roughness data obtained from at-line Raman and NIR spectroscopic and photometric imaging measurements to predict flow properties and residual moisture content of continuously produced granules. All three PAT tools measure different granule properties, which all might contribute to granule flowability and downstream processability.

MATERIALS AND METHODS

Materials

Anhydrous theophylline (Farma-Quimica sur SL, Malaga, Spain) (30%, w/w) was granulated with lactose monohydrate 200 M (Caldic, Hemiksem, Belgium). Polyvinylpyrrolidone (Kollidon 30, BASF, Burgbernheim, Germany) was added as a binder to the dry powder mixture in a concentration of 2.5% (w/w). Distilled water was used as granulation liquid. Sodiumlaurylsulfate (Fagron, Waregem, Belgium) was added to the granulation liquid (0.5% w/v) to improve the wettability of the dry powder mixture.

Methods

Wet granulation

All granules were produced using the ConsiGma™-25 unit (GEA Pharma Systems, Collette™, Wommelgem, Belgium), which consists of three major parts: a continuous twin screw high shear granulator, a six parallel cell fluid bed dryer and a discharge system. The equipment was already extensively described by Fonteyne et al. [5].

In order to obtain granules with different characteristics, a 3-factor full factorial design of experiments (DOE) was performed in randomized order (Table 1). The temperature of the granulator barrel, the powder feed rate and the temperature of the drying air were varied in order to obtain granules of different size distributions, solid state and moisture content. Preliminary experiments showed that – besides the screw configuration – these three factors significantly influenced the granule properties [5, 23]. The screw speed was held constant at 950 rpm and granulation liquid was added (9.16% (w/w), based on the wet mass). For each experiment, one drying cell of the six-segmented fluid bed dryer was filled with 1 kg of granules and an airflow of 400 m^3/h was used.

Photometric imaging technique

A photometric stereo camera system (FlashSizer3D, Intelligent Pharmaceutics Ltd, Finland) was used for particle size measurement and surface characterization (roughness and shape) of the produced granules. All data were collected using the FlashSizer3D Process Interface Software. The size ranges used for the calculation of the particle size distribution were: 0-150 µm, 151-250 µm, 251-500 µm, 501-710 µm, 711-1000 µm, 1001-1400 µm, 1401-2000 µm and 2001-3150 µm and >3150 µm. The FlashSizer 3D was equipped with a steel chute and glass window. The produced granules were poured into this chute and images were taken through the glass window. Due to the high amount of fines, which were present in most granule loads of the design experiments, the glass window of the imaging system was covered by fines, which resulted in an underestimation of the granules' particle size. Therefore, during each DOE experiment granules were, prior to the measurement, carefully derived from the manufacturing line into transparent rectangular plastic flasks, by means of a glass funnel. Three samples were collected per DOE experiment and each sample was analyzed in triplicate using the calculation mode "3D Surface", which calculates the particle size and global image roughness as described by Soppela et al. [15]. The averages of these nine granule size distribution and roughness measurements per DOE experiment were then used for data interpretation. Data were Unit Variance (UV)-scaled before applying PCA.

Raman spectroscopy

A RamanRxn1 spectrometer (Kaiser Optical Systems, Ann Arbor, Michigan), equipped with an air-cooled CCD detector (back-illuminated deep depletion design) was used with a fiber-optic non-contact MR probe. The laser wavelength was the 785 nm line from a 785 nm Invictus NIR diode laser. For each DOE experiment 20 spectra were statically recorded at-line with a resolution of 4 cm^{-1} and an exposure time of 20 seconds, using a laser power of 400 mW. Data collection and data transfer were automated using the HoloGRAMS™ data collection software and the HoloREACT™ reaction analysis and profiling software. The spectral data were centered and Standard Normal Variation (SNV) corrected before applying PCA.

NIR spectroscopy

A Fourier-Transform NIR spectrometer (Thermo Fischer Scientific, Zellik, Belgium, Nicolet Antaris II near-IR analyzer) equipped with an InGaAs detector, a quartz halogen lamp and a fiber optic diffuse reflectance probe was used. Again, 20 spectra of each granulation experiment were statically collected at-line in the 4500 - 10000 cm^{-1} region with a resolution of 16 cm^{-1} and averaged over 16 scans. Data collection and data transfer were done using Thermo Fischer Scientifics' Result Software. NIR spectra were centered and SNV-corrected prior to chemometric analysis.

Residual moisture determination

The residual moisture content of the granules of each DOE experiment was determined by volumetric Karl Fischer titration using a V30 volumetric KF titrator (Mettler Toledo, USA). Methanol (Hydranal, Sigma Aldrich, Germany) was used as a solvent. Before titration, approximately 50 mg of granules were stirred and dissolved in methanol during 5 minutes. Measurements were performed in triplicate.

Granule flow measurements

After production, the bulk density, tapped density and Hausner ratio of each DOE experiment were determined. Approximately 40 g of granules were poured into a 100 ml graduated cylinder. The granule weight and volume were used to calculate bulk density. Then, each sample was tapped 1250 times using an automatic tapping instrument (J. Engelsmann AG, Ludwigshafen am Rhein, Germany and the volume reading was then used to determine the tapped density. All density measurements were performed in triplicate and the average density was calculated. Bulk and tapped densities were used to determine granule flow characteristics via calculation of Hausner ratio values.

Data analysis

Several principal components analysis (PCA) and partial least squares (PLS) models were developed using a multivariate data analysis software package (Simca P+ 12.0, Umetrics AB, Umeå, Sweden). PCA was performed on all collected NIR and Raman spectra and imaging data to gain a first insight into the variation between the differently processed granules. Afterwards three prediction models were built by means of PLS regression as an attempt to predict moisture content, Hausner ratio and bulk and tapped density of the granules (Y) from the combined spectral and FlashSizer information (X). The number of PCA and PLS components was selected as such to obtain the highest Q^2 value, being the part of the total variation of X (PCA models) or Y (PLS models) that can be predicted by a component, as estimated by cross-validation.

RESULTS AND DISCUSSION

Principal Component Analysis

PCA was applied on the spectral data of all 220 observations (20 spectra per DOE experiment, 11 DOE experiments) to investigate the spectral variation caused by differences in solid-state properties and moisture content of the differently prepared granules.

Raman spectroscopy

The spectral region from 200 cm^{-1} to 1800 cm^{-1} was selected to perform PC analysis on all collected and SNV preprocessed Raman spectra. Four principal components described 97.6% of the spectral variation. The first, second, third and fourth PC explained 47.12%, 26.95%, 16.24% and 7.25 %, respectively. Figure 1 shows the PC 1 versus PC 2 scores plot. Two obvious clusters were identified. Cluster A contains all granules dried at 55°C and 75°C, whereas cluster B derived from granules dried at 35°C. The same clusters were obtained by plotting PC 2 versus PC 3 (Figure 2).

To explain why these two groups are clustered one should look at the loadings. Meaningful information regarding the solid state of theophylline can for example be found in the spectral range from 1636 cm^{-1} to 1737 cm^{-1}. The spectrum of anhydrous theophylline shows two intense peaks at

1664 and 1706 cm^{-1}, whereas theophylline monohydrate has a peak at 1686 cm^{-1}, which is due to C=O stretch of the carbonyl-groups [24]. Dukic-Ott et al. [25] presented the Raman-spectrum of metastable theophylline, showing a signal at 1692 cm^{-1}. The PCA loadings plots of PC 1, PC 2 and PC 3 at this spectral region (1636 cm^{-1} to 1737 cm^{-1}) can be found in Figure 3. The positive and negative peaks in the loadings plots of PC 1, PC 2 and PC 3 are listed in Table 2. Cluster A has mainly positive PC 1 and PC 2 score values, while cluster B has mainly negative PC 1 (except for DOE experiment 1) PC 2 score values. Hence, Cluster A mainly contains anhydrous and metastable theophylline granules, whereas cluster B mainly contains granules with theophylline monohydrate. The applied ConsiGma™-25 unit uses untreated ambient air for drying. At ambient inlet air, metastable theophylline will only occur at elevated temperatures (50° and up) whereas at lower temperatures the granules will hardly dry and stay in the monohydrate-form [23]. Cluster A contains DOE experiments 2, 3, 4, 5, 8, 9 and 10, which were all dried at 55° or 75°C, resulting in granules consisting of anhydrous and metastable anhydrous theophylline. Cluster B includes experiments 1, 6, 7 and 11, dried at 35°C, which is not high enough to remove the hydrate water from the granules.

In cluster B, the PC 1 score values of experiment 1 (red full triangles, Figure 1) are positive, unlike the score values of the other experiments of cluster B. Furthermore, the PC 3 score values of experiment 1 are clearly positive as well. This indicates that the granules of experiment 1 contain a significant amount of anhydrous theophylline besides theophylline monohydrate. This can clearly be seen in the Raman spectra of experiment 1, showing distinct anhydrous theophylline signals at 1664 and 1706 cm^{-1} and 555 cm^{-1} besides the monohydrate signal at 1686 cm^{-1} (Figure 4). The residual moisture content of the granules of all experiments was measured directly after drying (Table 3). Indeed, experiment 1 was found to have a slightly lower moisture content (5.43%) after drying compared to the other three experiments of cluster B (6.38%, 6.76% and 6.62%). Earlier work performed on the ConsiGma™-25 system revealed that small amounts of theophylline can remain anhydrous after wet granulation, when high barrel temperatures and high powder feed rates are applied (as is the case for experiment 1) [5]. Hence the significantly larger amount of anhydrous theophylline might not be

caused by the drying process, but might be a matter of formation of smaller amounts of theophylline monohydrate in the first place. In cluster A, experiment 2 has higher PC 3 score values (green full dots) compared to the other experiments of cluster A (Figure 2). This indicates that run 2 contains more anhydrous theophylline and less metastable theophylline compared to the other experiments of cluster A. Again, this was confirmed by the pure Raman-spectra of the granules in cluster A (spectra not shown).

NIR spectroscopy

The spectral region from 8500 cm^{-1} to 4500 cm^{-1} was taken into account to perform a PC analysis on all collected NIR spectra, resulting in three principal components. These explained 96.8 % of the spectral variation. PC 1 explained 69.34 % of the spectral variation, PC 2 21.19% and PC 3 6.24%. In Figure 5, the PC 1 versus PC 2 scores plot shows two distinct clusters along the PC 2-axis. Cluster B, having positive PC 2 score values, comprises experiments 1, 6, 7 and 11, whereas cluster A has negative PC 2 score values. The loadings plot (Figure 6) of the second principal component shows a positive band at 5068 cm^{-1} and 6749 cm^{-1}, which can be attributed to the hydrate water of theophylline monohydrate [26]. This confirms the Raman analysis, which also showed that experiments 1, 6, 7 and 11 resulted in granules containing theophylline monohydrate. Furthermore, these granules contain higher residual moisture after drying, as is confirmed by the Karl Fischer moisture determinations (Table 3). One run in cluster A tends to be partly in the positive part of the PC 2-axis, namely run 3 (full blue squares). This can easily explained by means of the Karl Fischer values, run 3 has the highest moisture content after drying compared to the other granules of cluster A.

In the near infrared region, water has large absorption bands. In particular the combination bands of O-H are very strong. The wavenumber and width of these bands may vary slightly, depending on the chemical and physical environment. Maxima were for example found around 7042 cm^{-1} (overtones) and 5208 cm^{-1} (combination bands) [27]. Rasanen et al. [26] reported the bands of free water

around 7092 cm^{-1} and 5249 cm^{-1}. They also describe how free water can be distinguished from hydrate water in the 2nd derivatives of the NIR spectra of theophylline granules by means of the free water band around 5249 cm^{-1} and a hydrate band around 5070 cm^{-1}. Furthermore, Luukkonen et al. [28] describe that lactose monohydrate shows a hydrate band around 5168 cm^{-1}. The 2nd derivatives of all collected NIR spectra of the DOE experiments clearly show a *lactose* monohydrate signal around 5168 cm^{-1} while only experiments 1, 6, 7 and 11 show a theophylline monohydrate signal around 5068 cm^{-1} (Figure 7), confirming the Raman findings. Free water bands cannot be seen in any of the NIR spectra.

Particle size distribution and roughness

The FlashSizer 3D process analyzer provided granule size distribution and granule surface roughness information. A PC analysis was performed on the imaging data of all 11 DOE experiments. The granule size distributions were derived from nine sieve fractions (see method section) and one average roughness value was obtained per experiment, leading to an 11x10 data matrix. PCA resulted in a three component model, explaining 73.35% (PC 1), 17.88% (PC 2) and 6.26% (PC 3) of variation respectively. The PC 1 versus PC 2 scores plot shows 4 clusters: a cluster containing experiments 9 and 11; a cluster containing experiments 5, 7 and 8; a cluster containing experiments 1, 2, 3 and 10 and a cluster containing experiments 4 and 6 (Figure 8). The clustered experiments indicate granules having similar size and roughness properties, whereas those experiments which are located far from each other are dissimilar with respect to granule size distribution and roughness values. The PC 1 versus PC 2 loadings plot displays the relationships between all 10 variables (9 sieve fractions + 1 roughness value) at the same time (Figure 9). The variables contributing similar information are grouped together, meaning they are correlated. The lower sieve fractions (< 150 µm, 150-250 µm and 250-500µm) are positively correlated. A similar conclusion can be made for the higher sieve fractions. Furthermore, the roughness value is positively correlated with the higher sieve fractions, indicating that higher roughness values are obtained for larger granules. This is expected as

the roughness value is a value describing the global roughness of the image. When there are larger particles present there is more shading effect, thus more variation in the surface images. Finally, Figure 9 shows that the lower and higher sieve fractions are negatively correlated, indicating that when the amount of fines (0-250 µm) decreases, the amount of oversized granules increases (> 1400 µm), and vice versa. This also suggests that increasing or decreasing the amount of fines and oversized granules does not affect the yield (150 µm < yield < 1400 µm). The distance of the variables to the origin of the loadings plot also conveys information. The further away from the plot origin a variable is situated, the stronger impact that specific variable has on the model. Figure 9 shows that all variables have similar distances to the plot origin, indicating that all variables have a similar impact on the model. To conclude, the first PC seems to explain the variability in fines and oversized granules, while the second PC reflects the yield. Figures 8 and 9 together show that experiments 9 and 11 result in granules having a large oversized fraction and a high roughness value. Experiments 5, 7 and 8 also result in more oversized granules, but have a larger yield fraction compared to experiments 9 and 11. Experiments 4 and 6 result in granules with a large fine fraction, while experiments 1, 2, 3 and 10 result in granules having the largest yield fraction. Experiments 4 and 6 also have the lowest roughness value. After tapping the granules of these runs they have the highest densities of all experiments (Table 3). This indicates that fines can fill the cavities in between larger granules. This leads to a flatter surface at the side of the rectangular plastic flask, which results in a smoother picture and hence a lower roughness value.

Partial Least Squares Modeling

This paragraph evaluates the possibility of using the complementary physical and chemical granule information (granule size distribution, shape, solid state) supplied by the at-line measurements for the prediction of critical granule properties, such as residual moisture content and flow properties. Therefore, three PLS-models were developed and evaluated. The NIR and Raman spectra, as well as the imaging data (granule size distribution and roughness values) and the process settings of the DOE

experiments were used as X-variables (Figure 10). For the Raman and NIR data, the score values of the principal components of their PCA models (cfr. supra) were included in the X-matrix. Twenty Raman and NIR spectra were collected after each granulation run, resulting in 220 rows (i.e., 11 granulation runs x 20 spectra) for the X-matrix. From the imaging data, the per DOE experiment averaged granule size distribution values and roughness values were used. The DOE process settings, being the temperature of the granulator barrel, the powder feed rate and the temperature of the drying air, completed the X-matrix. PLS models for moisture content, flowability (Hausner ratio) and density were developed separately and evaluated based on their predictive performance after cross-validation. Cross-validation was done as follows: (1) $1/7^{th}$ of the data was kept out of the model development; (2) the data which were kept out were then predicted by the model: (3) the predictions of the kept out data were compared with the actual values. This procedure was repeated for the seven groups [29].

The model for moisture content resulted in 3 PLS-components, explaining 96.4% of the variation (R^2). The fraction of the total variation of Y that could be predicted by the model (Q^2) was 96.2%. The model resulted in a Root Mean Square Error of Estimation (RMSEE) of 0.193 %. The loadings line plot of the first PLS-component (Figure 11) suggests that the score values of the second PC of the NIR PCA model are positively correlated to the residual moisture content, while the score values of the first and second principal component of the Raman PCA model together with the temperature of the drying air are negatively correlated to the residual moisture content.

The influential effect of the score values from the second principal component of the NIR PCA model can simply be explained by the fact that this 2^{nd} PC differentiates between theophylline spectra with and without hydrate-water. Indeed, the granules containing theophylline monohydrate have higher residual moisture contents (Table 3). The importance of the score values of the first and second principal component of the Raman PCA model can be explained using Table 2. These two Raman PCA model principal components differentiate between granules containing theophylline monohydrate

and granules without theophylline monohydrate. Hence, one can say that the higher the amount of theophylline monohydrate in the granules, the higher the residual moisture content will be. The negative loadings value for the drying temperature for the first PLS component shows that a high temperature of the drying air will result in a lower residual moisture content of the end product.

A second PLS-model was developed in order to predict the density of the granules (Y), taking both bulk and tapped density into account. The model, consisting of 3 PLS-components, had an R^2 of 91.9% and a Q^2 of 91.8%. The RMSEE was calculated to be 0.00476 g/ml for the bulk density and 0.0104 g/ml for the tapped density. The loadings line plot of the first PLS component (Figure 12) shows correlation between particle size distribution and bulk and tapped density. A positive correlation of the fines and smaller granules (<710 µm) and a negative correlation of the larger particles confirm that small particles can be more easily packed than large particles. Furthermore, the roughness value is negatively correlated with the density, since granulation experiments resulting in larger granules have high roughness values, which is resulted from the less densely packed powder bed surfaces (cfr. supra). The negative correlation of both barrel temperature and powder feed rate with the density parameters can be explained by the fact that larger granules are obtained when high barrel temperatures and high powder feed rates are applied [5].

A last PLS model was developed for Hausner ratio (Y), resulting in four PLS-components, explaining 93.9% of the variation. The fraction of total variation in the Y-matrix that could be predicted was 93.4%. Plotting the observed versus the predicted Hausner Ratio's resulted in an RMSEE of 0.00553. According to the loadings line plot of the first PLS component (Figure 13), correlation between the FlashSizer data and the Hausner ratio can be seen. The fines and small particles (< 710 µm) have a clear positive correlation with the Hausner ratio. The higher the Hausner ratio is the poorer granules will flow. Indeed, fines will decrease the flowability of the granules. On the other hand, larger granule sizes (710 µm and more) are negatively correlated to the Hausner ratio, as larger granules have a better flowability [3]. The roughness value is negatively correlated with the Hausner ratio as well. It

was stated earlier (PSD and Roughness section) that granulation experiments leading to granules with a low roughness value contain more fines, which indeed results in a poorer flowability and a higher Hausner ratio. Finally, the barrel temperature, and to a lesser extent the powder feed rate have a negative influence on the Hausner ratio since a high barrel temperature and a high powder feed rate result in larger granules (i.e., a lower Hausner ratio).

CONCLUSION

This study proves the utility of three PAT-tools for the at-line analysis of continuously produced granules. Data were recorded with both a Raman and an NIR spectrometer next to a photometric imaging technique. The residual moisture content was mostly correlated with the NIR spectroscopic data, whereas the imaging-data had the highest predictive capability for the flowability of the granules. Hence, the information offered by the spectrometers and the photometric imaging technique is complementary.

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